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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/238,405	05/05/1994	DANIEL J. CAPON	CELL5.3	5729

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	08/238,405	CAPON ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *remand filed 8/31/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57,59,64,65,67 and 69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57,64,65,67 and 69* is/are rejected.

7)☒ Claim(s) *59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Prosecution on the merits of this application is reopened on claims 57, 59, 64, 65, 67 & 69, in order to better explain the rejections made of record for The Board.

2. Claim 59 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

3. Claims 57, 64-65, 67 & 69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application exists for the broader and generic negative recitation of "in the absence of a T-cell receptor" (see Appendix C). In contrast, the proper context described in the paragraph bridging pages 30 & 31 of the specification is that a "CD8/ ζ" chain can be used as the cytoplasmic signaling domain in a Jurkat T cell leukemic line, JRT3.T3.5, which contains a mutated and non-functional T-cell receptor (see Appendix B). T-cell lines, by definition, contain a T-cell receptor (see Appendix A). Mutated T-cell lines contain mutated T-cell receptors (i.e., as it relates to Jurkat T cell leukemic line, JRT3.T3.5). In other words, a T-cell receptor still exists in these cells, which is no longer functional, presumably until the CD8/ ζ (zeta) chain is added. See Appendix B. Therefore, the broader and negative

recitation of excluding any T-cell receptors in those cells that are required for making the claimed chimeric receptor protein with a transmembrane domain was not reasonably contemplated at the time of filing Appellants' invention; thereby, constituting new matter.

No proper antecedent basis further exists for using any "cytoplasmic domain", as recited in claim 57, for making the claimed chimeric receptor protein at the time of filing the instant application. Only the "CD8/ ζ" chain" cytoplasmic domain was contemplated for use with a mutated T-cell receptor containing cell. Therefore, "cytoplasmic domains" selected from the group consisting of the CD3 zeta chain, the CD3 eta chain, the CD3 gamma chain, the CD3 epsilon chain, the gamma chain of the Fc receptor and tyrosine kinase", as currently recited, also constitute new matter for those claims which do use a normal cell to make the claimed receptor protein.

It is again noted that if claim 57 recited "a cytoplasmic domain...in the absence of a wildtype T-cell receptor expressed on the cell surface, wherein said cytoplasmic domain consists of a CD8 ζ (zeta) chain, and when said chimeric protein is then expressed as a membrane bound protein...", this rejection may be obviated. It is acknowledged Appellants are correct that the zeta chain is of the T-cell receptor (Tc receptor) and not of the Fc receptor.

Appellants' arguments in the Brief related to "in haec verba support" are not on point because Appellants are not allowed to change the scope and conception of the invention, in order to overcome the previous prior art made of record (i.e., the rejection of claims 57, 64, 67, 69 & 71 under 35 U.S.C. 102(b) as being anticipated by Gross et al. in Paper NOs: 27 & 30 (mailed 9/08/98 & 5/26/99) solely because of the absolute recitation of "in the absence of a T-cell receptor". The issue is simple. Pages 30-31 of the specification solely contemplate transfection of a CD8/ ζ (zeta) chain of the "Tc receptor " into a mutated T-cell Jurkat cell line, where the

issue then becomes whether the generic negative limitation of "in the absence of a T cell receptor" is properly contemplated in order to overcome the previously cited 102(b) art. In contrast, it is not reasonable to extrapolate from the limited disclosure of using a mutated cell line where a mutated and nonfunctional T-cell receptor is expressed to now exclude prior art by reciting the absolute concept of using any "cytoplasmic domain" "in the absence of a T cell receptor"; thereby, still constituting new matter for the different invention now claimed.

4. Claims 57, 64, 67 & 69 stand rejected under 35 U.S.C. 102(e) as being anticipated by Eshhar et al. (U.S. Patent 5,906,936).

Eshhar et al. teach creation of a membrane bound chimeric antibody (Ab)/ T-cell receptor (TcR) chimeric protein (i.e., still containing the T-cell receptor-derived tyrosine kinase activity; as it relates to claim 57), in which the extracellular TcR V[ariable] domain (i.e, α and β chains) are replaced with either the extracellular "variable... heavy (H) or light (L) chain" of a "antibody for a predefined antigen" (i.e., a single chain antibody variable (V) domain; column 4 (lines 18-29 & 6-9); columns 5-7; Figure 4; as it relates to claim 57). In other words, Eshhar's chimeric protein must be created in a cell in order to be expressed on the surface of a cell and "comprise" in the N-terminal to C-terminal region an "extracellular antigen-binding domain" region naturally joined to the "transmembrane domain" of the "TcR/CD3" receptor (column 3, line 66), and then to a TcR/CD3 "cytoplasmic domain" comprising the constant region of the T-cell receptor, γ and/or δ chains (e.g., column 4, lines 6-7; column 6 & Figures 8-9), which thereby "initiates/transduces a signal resulting in activation of a secondary messenger system (i.e., as evidenced by IL-2 production in the MTT assay; Table I, Figures 1 & 4; column 2; and where "stimulation through the cTcR triggered the T cell hybridoma to its full activity"; column

10, lines 9-11; as it relates to claim 57). In that Eshhar also teach making their chimeric protein construct in mutated human/ mammalian Jurkat T-cells, such as in column 9 (line 64), which describes use of "a TcR [T-cell receptor] deficient mutant (27J)" (i.e., this particular mutant contains no T-cell receptor; see Appendix C), and Table I, which demonstrates use of the cytotoxic T lymphocyte "(CTL) hybridoma lacking the TcR chain" (i.e., no T-cell receptor, by definition; see Appendix C) where neither of these cell lines would be recognized as foreign in an appropriate host due to them being "not-restricted by self-MHC molecules" (e.g., see column 10, line 52-54; column 2, lines 26-31; as it relates to claim 69), the limitation of "in the absence of a T-cell receptor" (i.e., as it relates to claims 57) and claims 64, 67 & 69 are anticipated, because the CTL hybridoma cell is specifically stated to "lack... the TcR chain" (i.e., see Appendix C).

In contrast to Appellants' arguments, no where is any structure recited in the claims (e.g., SEQ ID NO) that distinguishes use of Eshhar's gamma (γ) and delta (δ) chains from that of the instant invention, which alternatively appear to be identical to that recited in the claims. In other words, Appellants' supposition that "[t]he gamma and delta chains of Eshhar et al. are not the same as the CD3 gamma and CD3 delta chains of the instant invention" has no definitive support, and simply is incorrect; especially when taken into account that Eshhar's gamma (γ) and delta (δ) chains are derived from the same T-cell receptor (TcR)/ CD3 as that claimed (e.g., see column 3, last paragraph; column 9, lines 3-6). Thus, Appellants' arguments are not on point with that currently claimed.

In summary, because Eshhar's chimeric protein "initiates/ transduces a signal resulting in activation of a secondary messenger system (i.e., as evidenced by IL-2 production in the MTT assay; Table I, Figures 1 & 4; column 2), Eshhar et al. obviously teach the same CD3 gamma

and delta chains as in the instant invention, because otherwise, no signal for Il-2 secretion would be transduced/ initiated; consistent with that stated by Weiss.

Lastly, Appellants' argue that "it is clear that because Eshhar et al. is essentially shuffling variable and constant domains between immunoglobulin and immunoglobulin-like molecules such as alpha, beta, gamma and delta chains of Ti, Eshhar et al. clearly is distinct from the instant invention". In contrast to Appellants' assertions, Eshhar et al. specifically disclose that "according to the present invention, there were constructed chimeric T cell receptor genes by recombining the V_H and V_L gene segments of an anti-TNP antibody with the constant region exons of the T cell receptor's (TcR) α and β chain" (column 3, lines 42-46), which clearly meets the limitations for "a chimeric protein *comprising* in the N-terminal to C-terminal region an extracellular antigen-binding domain of a single chain antibody that binds specifically to an antigen [emphasis added]" (e.g., TNP). Second, consistent with Appellants' discussion on pages 10-13 of the brief, Eshhar et al. teach that "[a]lthough ligand binding to the T cell receptor initiates two early activation signals (calcium raised and PKC activation) as reviewed in Weiss et al...., they are not sufficient to cause IL-2 production and proliferation of T cells...". Lastly, Appellants argue on page 19 of the brief that Eshhar's host cells "express T cell receptor". In contrast to this assertion, Eshhar et al. also teach making their chimeric protein construct in mutated human/mammalian Jurkat cells (e.g., column 9, line 64), using "a TcR [T-cell receptor] deficient mutant (27J)", and/or the cytotoxic T lymphocyte (CTL) hybridoma, lacking the TcR chain (Table I; see Appendix C). Therefore, Appellants' arguments that Eshhar's host cells all "express T cell receptor" are simply misleading and not on point. Again, it is noted that the sole reason Gross et al was removed as 102(b) prior art was because they did not specifically disclose use of a "TcR deficient mutant", unlike Eshhar et al. ('936).

In conclusion, Eshhar ('936) teach the same as recited in claim 57 for a "chimeric protein comprising... an extracellular antigen-binding domain of a single chain antibody that binds specifically to an antigen... a transmembrane domain... a cytoplasmic domain which initiates a signal resulting in activation of a secondary messenger system in the absence of a T-cell receptor, wherein said cytoplasmic domain is selected for... the CD3 gamma chain, the CD3 delta chain... and tyrosine kinase", as claimed. Therefore, because no where in the current claims nor instant specification is there any recitation nor description of any structure (e.g., SEQ ID NO) that distinguishes the instant invention from Eshhar's chimeric protein, and because Appellants' arguments center on α and β subunits and sections of Eschar et al. not relied upon for the instant rejection (e.g., as argued on pages 18-19 of the Brief), there is no distinction between Eshhar's chimeric receptor protein, and that claimed.

Accordingly, it is noted that the courts have held that:

"the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray,* 10 USPQ 2d 1922 (1989); *In re Best,* 195 USPQ 430 (CCPA 1976).

Further, the courts have held that "when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product..., a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable". *In re Brown*, 173 USPQ 685 (1972).

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

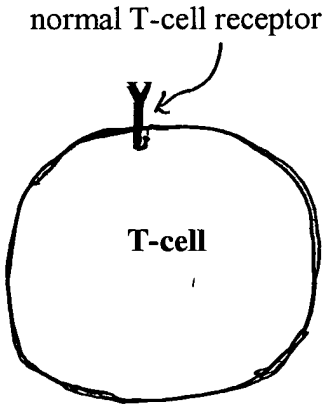
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
February 28, 2007

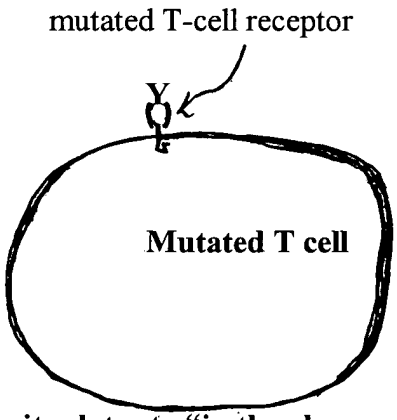
ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER

APPENDICES:

A. wildtype T-cells



B. The Examiner's interpretation of a Jurkat T cell mutant



C. The Examiner's interpretation of that claimed (i.e., as it relates to "in the absence of a T cell receptor